REMARKS

1. Priority Application

The Examiner has acknowledged Applicant's claim for foreign priority based on an application filed in Panama on 21 February, 2000. Applicant would like to point out that Applicant's claim to priority was based on a US provisional application (Ser. No. 60/186,295) filed March 1, 2000 under 35 U.S.C. §119(e) and a Danish patent application ("PA"), PA 2000 00265 filed on February 21, 2000 under 35 U.S.C. §119(c). A certified copy of the Danish priority application is attached hereto. Applicant believes that its priority claim has now been perfected.

2. Oath/Declaration

The Examiner has objected to the oath/declaration because it refers to an incorrect application number "009/785215". Applicant has enclosed a new oath/declaration which properly refers to the instant application. Reconsideration and removal of the objection is respectfully requested.

3. Specification

The Examiner has objected to the Specification because the disclosure's discussion of the figure on page 17 should be entitled "Brief Description of the Figure", the sentence on page 25, line 18 and page 61, line 31 do not end in periods and the word "structure" on page 49, line 7 is misspelled. Applicant has corrected these informalities. Reconsideration and removal of the objections is respectfully requested.

4. Claim Objections

Claims 1-29, 33 and 59-67 have been objected to for reciting non-elected material. Applicant has amended the claims so that they no longer recite non-elected material. Reconsideration and removal of the objection is respectfully requested.

5. Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 11 and 22 have been rejected as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 1 has been rejected for reciting a broad range together with a narrow range or limitation that falls within the broad limitation. Applicant has removed the limitation "including a human being" from claim 1 to obviate this rejection. Claim 11 was rejected because the limitation "the natural T-cell epitope" in the second line did not have proper antecedent basis support. Applicant has amended claim 11 to substitute the word "foreign" in place of "natural". The term "foreign T-helper cell epitope" find proper antecedent basis support in claim 10. Finally, claim 22 was rejected for referring to "Fig. 1" in the claim. Applicant has cancelled claim 22 thereby rendering the rejection moot. Applicant believes that the foregoing amendments have overcome all of the indefiniteness rejections. Reconsideration and removal of the rejections is respectfully requested.

6. Rejections under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1-29, 33 and 59-67 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In paragraph 14 on page 7 of the Office Action, the Examiner argues that while general guidance is given in the Specification on the use of a fragment of SEQ ID NO: 2 to make antibodies, no working examples are given re: vaccination of subjects using the SEQ ID NO: 2 fragment, other fragments of SEQ ID NO:2, analogues of SEQ ID NO: 2 or the 672-714 fragment, or a specific immune response elicited by the SEQ ID NO: 2 fragment which leads to an *in vivo* down-regulation of amyloid protein. The Examiner, therefore, concludes that the claimed invention directed to using Aβ peptide to produce an in vivo down-regulation of amyloid protein in an animal is not supported by the teachings of the Specification or the prior art (Tennent et al., 1995; Stein and Johnson, 2002). The Examiner further argues that the claimed invention is not enabled by the Specification because the skilled artisan would be expected to doubt that the claimed method would work due to the following obstacles: the effects of an immune response to an antigen, expectation that the Aβ peptide

would be actively involved in amyloid deposition as opposed to being a non-dynamic component (US Patent 5,851,996; Perutz et al., 2002), how does the immunogenic effect on amyloid deposition relate to symptoms of amyloid-related diseases and specific biological actions/activities that the antigenic composition of Aβ peptide and an adjuvant would effect. Applicant respectfully traverses.

As a preliminary matter, Applicant notes that the Examiner has used a number references which were published well after Applicant's priority date, February 21, 2000 to support his arguments that the claims are not enabled. It is well settled that Examiners should not use post-filing date references to demonstrate that the patent (or application) is not enabling (see MPEP 2164.05(b)). Examiners may use such references if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective date of the patent application. However, publications dated after the filing date, that provide information publicly first disclosed after the filing date, generally cannot be used to show what was known at the date of filing. Applicant submits that the Examiner has improperly cited references that provide information publicly first disclosed after the filing date to show what was known at the date of filing. As such, Applicant submits that many of the Examiner's arguments in paragraphs 11-25 regarding lack of enablement which rely on such later-filed references are improper and should be withdrawn.

Applicant would first like to point out that the claims have been amended and are now directed to a method of down-regulating autologous Aβ or autologous amyloid precursor protein (APP). The present invention first and foremost addresses the problems discussed in the specification on page 78, first full paragraph. That is, not only is it essential to down-regulate Aβ via active immunotherapy, but it is of equal interest to avoid the problems of generating uncontrolled autoimmunity that targets T-cell epitopes present in autologous Aβ.
The prior art referred to in the specification (especially the Schenk et al, 1999 paper) relies on immunization with unmodified wild-type Aβ formulated in a strong adjuvant. Use of the unmodified wild-type Aβ formulation in subsequent clinical Phase II trials had to be stopped due to problems with neurotoxicity. These problems were later demonstrated to be the consequence of uncontrolled T-cell immunity that targets Aβ, cf. McLaurin *et al.* 2002 (enclosed).

The present invention, in contrast, focuses on the use of *modified* Aβ and APP as the immunogen, wherein the modification entails using a foreign T_H epitope. The inventors have gone to great lengths to establish that such constructs are superior to native Aβ with respect to 1) their ability to break B-cell autotolerance and 2) their *inability* to induce T-cell autoreactivity. In other words, according to the present invention, the safety of the immunogen is ensured by driving the T helper cell immune response by a foreign T helper cell epitope, meaning that no cellular immune responses are directed towards autologous molecules and cells. Hence, the immune response induced according to the present invention is a "clean" humoral immune response.

The "clean" humoral immune response achieved using the present invention is described in the enclosed 37 C.F.R. 1.132 Declaration of Peter Birk Rasmussen, a co-inventor of the instant invention. The enclosed Declaration addresses many of the points raised by the Examiner in paragraphs 11-15 of the Office Action. As can be seen from the enclosed declaration by Peter Birk Rasmussen, the inventors and their collaborators have performed a large number of experiments after the filing of the present application. These experiments were performed in mice and demonstrate that Aβ is effectively down-regulated in a number of animal models.

Two sets of experiments were performed under Dr. Rasmussen's supervision and control. In the first set, the effect of vaccination with the instant vaccines were compared against vaccination with a control against the Aβ-42 molecule to determine if the presently claimed approach to treat Alzheimer's disease is viable. The vaccines were made according to the teachings of the instant application and were tested in 2 studies in a transgenic mouse model of Alzheimer's disease. They were compared to the non-modified Aβ-42 wildtype protein vaccine described in Schenk, D. et al. (Nature, 400; 173-177 (1999). As testified to by Dr. Rasmussen, the amyloid plague burden is correlated to the state of progression of Alzheimer's disease and the presence of these plaques in the brain is used as a post-mortem diagnosis of the disease. The results reveal that several constructs according to the present invention generate significantly higher anti- Aβ titres than the control Aβ-42 wildtype molecule vaccine (see paragraph 7.8 of the Declaration) and significantly reduce plaque burden (see paragraph 7.10 of the Declaration).

The other objective was to demonstrate that the use of the claimed technology eliminates or reduces the risk of generating an auto-reactive T-cells specific for Aβ, as opposed to the non-modified wildtype Aβ-42 vaccine. The results indicate that the Aβ variant vaccines, unlike the wildtype Aβ-42 control vaccines, do not activate Aβ-42 specific T-cells (see paragraphs 8.6 and 11 of the Declaration.

The experiments described in Dr. Rasmussen's Declaration were designed to *verify* the teachings in the present application, *i.e.* that vaccination with Aβ variants or APP variants that include a foreign T_H epitope does indeed provide a safe and improved immune response against Aβ that can reduce plaque formation. Applicant submits that an artisan skilled in vaccine technology would have a reasonable basis to believe that the invention would work for its intended purpose after reading the instant Specification. The Declaration clearly establishes that the teachings in the application were sound. So, while the present application may not include working examples that demonstrate the efficacy of each and every embodiment, later experimentation has indeed demonstrated that the invention works as described by the inventors. Accordingly, Applicant submits that the claimed invention is clearly enabled by the Specification.

The Examiner has expounded at length as to why he believes the invention is not enabled or would require undue experimentation to practice the full scope of the invention. These comments are found in paragraphs 16-25 of the Office Action. Applicant disagrees with the Examiner's conclusions, but believes that further argumentation is unnecessary because the foregoing comments and the Declaration testimony of Dr. Rasmussen clearly demonstrate that the claimed invention is enabled thereby overcoming the outstanding rejection. However, Applicant submits the following remarks to completely and fully respond to the Examiner's comments in paragraphs 16-25. But, as one example of the incorrectness of the conclusions the Examiner has drawn in paragraphs 16-25, in paragraph 25, the Examiner argues that the application has failed to establish a nexus between the specific immune response recited in the claims and the down-regulation of amyloid protein recited in the claims. The Examiner argues that amyloid related disorders are varied and that it is not clear that Aβ would be sufficiently involved in a rate-limiting step for any amyloid related disorder such that it could be used to

elicit a specific and sufficient immune response to down-regulate amyloid protein thereby providing relief from an amyloid-related disorder or disease. Applicant disagrees! Even though the art has not fully established that Aβ is the cause of Alzheimer's disease, Applicant submits that there is sufficient circumstantial evidence that plaque reduction is beneficial in Alzheimer's disease – plaque reduction can simply be obtained by clearing Aβ, whereas it is not necessary to interfere with "activity" of Aβ. The Examiner appears to have set a new and arguably higher bar for applicants in this field. Meeting the Examiner's standard would necessarily require the completion of a phase II clinical trial. This is simply not required. Applicants are only required to describe their application in terms that will enable a person of ordinary skill in the art to practice the full scope of the invention. Applicant has met this burden. Applicant has described a method of down-regulating Aβ or APP in an animal by administering an immunogenically effective amount of an Aβ or APP analogue. Applicant has described why this method would be effective in treating various amyloid related disorders, such as Alzheimer's disease. In this context it does not seem fair to rely on some doubts expressed by some scientists without considering the efforts or results of other scientists engaged in research and development activities in the field. For example, it has recently been shown by a group from Harvard Medical School that the immune hypo-responsiveness toward Aβ-42 in Aβ Tg mice could be partially overcome by conjugating a B cell epitope (Aβ1-15) to BSA (Monsonego et al. (2001) 98(18), 10273-10278, enclosed). It was claimed that the decreased antibody response toward Aβ-42 in the human APP-Tg mice was not due to B cell tolerance but rather the inability of Aβ specific T cells to provide the necessary help for antibody production. Hence, PNAS found it worthwhile to publish a paper as late as in August 2001 where it is reported that inclusion of foreign T_H epitopes in an Aβ vaccine provides for an improved immunogenicity of the vaccine. These results indicate that the presently claimed approach is non-trivial. But, more importantly, the work of an independent group directly demonstrates and corroborates the presently claimed approach that the inclusion of foreign T_H epitopes (in this case by means of coupling to BSA) is an effective means to improve immunogenicity.

The foregoing remarks establish that vaccination with Aβ variants or APP variants that include a foreign T_H epitope provides a safe and improved immune response against Aβ that can

reduce plaque formation. Applicant submits that the skilled artisan would be able to prepare suitable Aβ variants or APP variants for use in the invention without undue experimentation using the teachings described in the Specification and generally available knowledge and techniques in the art. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

Favorable consideration and early allowance of all the claims is requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: June 19 2003
(Date of Deposit)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

(Signature)

June 19 2003
(Date of Signature)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____

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Attachment: Version with Markings to Show Changes Made
Declaration under 37 CFR 1.132
Certified Copy of Priority Document
Supplemental Oath/Declaration
PTO Form 1449

CHANGES MADE TO THE SPECIFICATION

On page 17, please replace the header "LEGEND TO THE FIGURE" with:

--BRIEF DESCRIPTION OF THE FIGURE—

On page 25, please replace the paragraph starting on line 10 with the following:

--"Stimulation of the immune system" means that a substance or composition of matter exhibits a general, non-specific immunostimulatory effect. A number of adjuvants and putative adjuvants (such as cytokines) share the ability to stimulate the immune system. The result of using an immunostimulating agent is an increased "alertness" of the immune system meaning that simultaneous or subsequent immunization with an immunogen induces a significantly more effective immune response compared to the isolated use of the immunogen.—

On page 49, please replace the first paragraph with the following:

--Yet another interesting way of modulating an immune response is to include the immunogen (optionally together with adjuvants and pharmaceutically acceptable carriers and vehicles) in a "virtual lymph node" (VLN) (a proprietary medical device developed by ImmunoTherapy, Inc., 360 Lexington Avenue, New York, NY 10017-6501). The VLN (a thin tubular device) mimics the ~~structrue~~ structure and function of a lymph node. Insertion of a VLN under the skin creates a site of sterile inflammation with an upsurge of cytokines and chemokines. T- and B-cells as well as APCs rapidly respond to the danger signals, home to the inflamed site and accumulate inside the porous matrix of the VLN. It has been shown that the necessary antigen dose required to mount an immune response to an antigen is reduced when using the VLN and that immune protection conferred by vaccination using a VLN surpassed

conventional immunization using Ribi as an adjuvant. The technology is *i.a.* described briefly in Gelber C *et al.*, 1998, "Elicitation of Robust Cellular and Humoral Immune Responses to Small Amounts of Immunogens Using a Novel Medical Device Designated the Virtual Lymph Node", in: "From the Laboratory to the Clinic, Book of Abstracts, October 12^{th} – 15^{th} 1998, Seascape Resort, Aptos, California".—

On page 61, please replace the paragraph beginning on line 12 with the following:

--The general outline of a vector of the invention comprises the following features in the 5′→ 3′ direction and in operable linkage: a promoter for driving expression of the nucleic acid fragment of the invention, optionally a nucleic acid sequence encoding a leader peptide enabling secretion (to the extracellular phase or, where applicable, into the periplasma) of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment of the invention, and optionally a nucleic acid sequence encoding a terminator. When operating with expression vectors in producer strains or cell lines it is for the purposes of genetic stability of the transformed cell preferred that the vector when introduced into a host cell is integrated in the host cell genome. In contrast, when working with vectors to be used for effecting *in vivo* expression in an animal (*i.e.* when using the vector in DNA vaccination) it is for security reasons preferred that the vector is incapable of being integrated in the host cell genome; typically, naked DNA or non-integrating viral vectors are used, the choices of which are well-known to the person skilled in the art.--

CLAIMS AS AMENDED BY RESPONSE

1. (Currently Amended) A method for *in vivo* down-regulation of autologous beta amyloid (Aβ) protein or autologous amyloid precursor protein (APP) in an animal~~, including a human being,~~ the method comprising effecting presentation to the animal's immune system of an immunogenically effective amount of

~~———~~at least one analogue of the animal's autologous Aβ or autologous APP~~amyloidogenic polypeptide~~ wherein is introduced at least one isolated foreign T helper epitope (T_H epitope) by means of insertion, addition, deletion, or substitution, or by means of separate coupling to a polyhydroxypolymer carrier backbone of the T_H epitope and an Aβ or APP derived peptide sequence, whereby ~~modification in the amino acid sequence of the amyloidogenic polypeptide which has as a result~~ immunization of the animal with the analogue induces production of antibodies against the autologous Aβ or autologous APP in the animal. ~~amyloidogenic polypeptide~~.

2. (Cancelled) ~~The method according to claim 1, wherein is presented an analogue with at least one modification of the amino acid sequence of the amyloidogenic polypeptide.~~

3. (Currently Amended) The method according to claim 1~~2~~, wherein the ~~modification~~ introduction ~~has as a~~ results in the preservation of ~~that~~ a substantial fraction of B-cell epitopes in ~~of the amyloidogenic polypeptide~~the Aβ or APP ~~are preserved~~ and ~~that~~wherein

~~——— at least one foreign T helper lymphocyte epitope (T_H epitope) is introduced, and/or~~

- at least one first moiety is introduced which effects targeting of the ~~modified molecule~~analogue to an antigen presenting cell (APC) or a B-lymphocyte, and/or

- at least one second moiety is introduced which stimulates the immune system, and/or

- at least one third moiety is introduced which optimizes presentation of the ~~modified amyloidogenic polypeptide~~analogue to the immune system.

4. (Currently Amended) The method according to claim 3, wherein the ~~modification includes~~analogue is modified by introduc~~tion as~~ing side groups, by covalent or non-covalent binding to suitable chemical groups in ~~the amyloidogenic polypeptide~~Aβ or APP, or a subsequence thereof, ~~of the foreign T_H epitope and/or~~ of the first and/or of the second and/or of the third moiety.

5. (Cancelled) ~~The method according to claim 3, wherein the modification includes amino acid substitution and/or deletion and/or insertion and/or addition~~.

6. (Cancelled) ~~The method according to claim 5, wherein the modification results in the provision of a fusion polypeptide.~~

7. (Currently Amended) The method according to claim ~~5~~1, wherein introduction of the amino acid substitution, ~~and/or~~ deletion, ~~and/or~~ insertion and/or addition results in a substantial preservation of the overall tertiary structure of ~~the amyloidogenic polypeptide~~Aβ or APP.

8. (Currently Amended) The method according to claim ~~2~~1, wherein the ~~modification~~ analogue includes a duplication of at

least one B-cell epitope of the amyloidogenic polypeptide and/or an introduction of a hapten.

9. (Currently Amended) The method according to claim ~~3~~1, wherein the foreign T-cell epitope is immunodominant in the animal.

10. ~~(Presently Amended)~~ (Currently Amended) The method according to claim ~~3~~1, wherein the foreign T-cell epitope is promiscuous.

11. (Currently Amended) The method according to claim 10, wherein the ~~natural~~foreign T-cell epitope is selected from a Tetanus toxoid epitope, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a *P. falciparum* CS epitope.

12. (Currently Amended) The method according to claim 3, wherein the first moiety is selected from a substantially specific binding partner for a B-lymphocyte specific surface antigen and a substantially specific binding partner for an APC specific surface antigen.

13. (Currently Amended) The method according to claim 3, wherein the second moiety is selected from a cytokine; a hormone, ~~;~~ and a heat-shock protein.

14. (Currently Amended) The method according to claim 3, wherein the third moiety is of lipid nature or wherein the third moiety is a polyhydroxypolymer.

15. (Currently Amended) The method according to claim 65, wherein the polysaccharide serves as a carrier backbone to which the ~~amyloidogenic polypeptide~~Aβ or APP derived peptide sequence and the foreign T cell epitope are separately bound.

16. (Currently Amended) The method according to claim 15, wherein the ~~amyloidogenic polypeptide~~Aβ or APP derived peptide sequence and the foreign T cell epitope are bound via an amide bond to the polysaccharide.

17. (Currently Amended) The method according to claim 1, wherein the autologous ~~amyloidogenic polypeptide or subsequence~~Aβ or APP ~~thereof~~ has been modified so as to preserve B-cell epitopes which are not exposed to the extracellular phase when present in a cell-bound form of the autologous APP~~precursor polypeptide for the amyloidogenic polypeptide~~.

18. (Currently Amended) The method according to claim 17, wherein the ~~amyloidogenic polypeptide~~autologous Aβ or APP has been modified so as to lack at least one B-cell epitope which is exposed to the extracellular phase when present in a cell-bound form of the ~~precursor polypeptide~~ autologous APP.

19. (Currently Amended) The method according to claim 1 which comprises a substitution of at least one amino acid sequence within ~~the amyloidogenic polypeptide~~autologous Aβ or APP with an amino acid sequence of equal or different length which gives rise to a foreign T_H epitope in the analogue.

20. (Cancelled) ~~The method according to claim 1, wherein the amyloidogenic polypeptide is selected from the group consisting of beta-amyloid (Aβ), amyloid precursor protein (APP), ApoE4, presenillin, a prion polypeptide, Alpha1-antichymotrypsin (ACT), Alpha2-macroglobulin, ABAD (Aβ-peptide binding alcohol dehydrogenase), APLP1 and -2 (amyloid precursor like protein 1 and -2), AMY117, Bax, Bcl-2, Bleomycin hydrolase, BRI/ABRI, Chromogranin A, Clusterin/apoJ,~~

~~CRF (corticotropin releasing factor) binding protein, EDTF (endothelial derived toxic factor), a heparan sulfate proteoglycans, human collapsin response mediator protein 2, huntingtin, ICAM I, IL 6, lysosome associated antigen CD68, P21 ras, PLC delta 1 (phospholipase C isoenzyme delta 1), Serum amyloid P component (SAP), Synaptophysin, Synuclein (alpha synuclein or NACP), TGF b1 (transforming growth factor b1), full length or a fragment of V domain of IG light chain, a 76 residue N terminal fragment of amyloid A protein, full-length or a fragment of transthyretin variants, an N-terminal fragment of ApoA1 variants, a full length lysozyme variant, a 37 residue fragment of islet amyloid polypeptide, a full-length wild type insulin, full length or a fragment of prion protein, a fragment of calcitonin, full length or a fragment of transthyretin, full length wild type β-2 microglobulin, atrial natriuretic factor, a 110 residue fragment of variant cystatin, a 71 residue fragment of gelsolin variants, and a fragment of fibrinogen α-chain variants.~~

21. (Cancelled) ~~The method according to claim 1, wherein the amyloidogenic polypeptide is (Aβ)~~.

22. (Cancelled) ~~The method according to claim 21, wherein the amino acid sequence containing the foreign T_H epitope is introduced into the amyloidogenic polypeptide as schematically shown for the P2 and P30 epitopes in Fig. 1.~~

23. (Previously Amended) The method according to claim ~~22~~1, wherein the ~~amyloidogenic polypeptide~~analogue comprises an amino acid sequence corresponding to amino acids 700-714 in SEQ ID NO: 2~~, such as an amino acid sequence consisting of amino acid residues 672-714 in SEQ ID NO: 2~~.

24. (Currently Amended) The method according to claim 23, wherein the ~~amyloidogenic polypeptide~~analogue comprises the amino acid sequence corresponding to amino acids 672-714 in SEQ ID NO: 2, wherein is inserted an amino acid sequence which gives rise to a foreign T_H epitope in the analogue, or wherein the ~~amyloidogenic polypeptide~~analogue comprises an amino acid sequence corresponding to amino acids 672-714 of SEQ ID NO: 2, wherein at least one amino acid sequence is substituted by an amino acid sequence of equal or different length so as to give rise to a foreign T_H epitope.

25. (Currently Amended) The method according to claim 1, wherein presentation to the immune system is effected by having at least two copies of the ~~amyloidogenic polypeptide, the subsequence thereof or the modified amyloidogenic polypeptide~~analogue covalently of non-covalently linked to a carrier molecule capable of effecting presentation of multiple copies of antigenic determinants.

26. (Currently Amended) The method according to claim 1, wherein the ~~amyloidogenic polypeptide, the subsequence thereof, or the modified amyloidogenic polypeptide~~analogue has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens.

27. (Currently Amended) The method according to claim 1, wherein an effective amount of the ~~amyloidogenic polypeptide or the analogue of the amyloidogenic polypeptide~~analogue is administered to the animal via a route selected from the parenteral route ~~such as the intradermal, the subdermal, the intracutaneous, the subcutaneous, and the intramuscular routes~~; the peritoneal route; the oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route.

28. (Currently Amended) The method according to claim 27, wherein the effective amount is between 0.5 μg and 2,000 μg of ~~the amyloidogenic polypeptide, the subsequence thereof or~~ the analogue ~~thereof~~.

29. (Currently Amended) The method according to claim 27, wherein the ~~amyloidogenic polypeptide or~~ analogue is contained in a virtual lymph node (VLN) device.

30. (Cancelled)

31. (Cancelled)

32. (Cancelled)

33. (Previously Amended) The method according to claims 22, which includes at least one administration per year.

34. (Cancelled)

35. (Cancelled)

36. (Cancelled)

37. (Cancelled)

38. (Cancelled)

39. (Cancelled)

40. (Cancelled)

41. (Cancelled)

42. (Cancelled)

43. (Cancelled)

44. (Cancelled)

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52. (Cancelled)

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54. (Cancelled)

55. (Cancelled)

56. (Cancelled)

57. (Cancelled)

58. (Cancelled)

59. (Previously Added) The method according to claim 10, wherein the foreign T-cell epitope is selected from a natural promiscuous T-cell epitope and an artificial MHC-II binding peptide sequence.

60. (Previously Added) The method according to claim 11, wherein the tetanus toxoid epitope is selected from P2 (SEQ ID NO: 4) and P30 (SEQ ID NO: 6).

61. (Previously Added) The method according to claim 12 wherein the specific binding partner is selected from a hapten and a carbohydrate for which there is a receptor on the B-lymphocyte or the APC.

62. (Previously Added) The method according to claim 13, wherein the cytokine is selected from the group consisting of interferon γ (IFN-γ), an effective part of INF-γ, Flt3L, an effective part of Flt3L, interleukin 1 (IL-1), an effective part of IL-1, interleukin 2 (IL-2), an effective part of IL-2, interleukin 4 (IL-4), an effective part of IL-4, interleukin 6 (IL-6), an effective part of IL-6, interleukin 12 (IL-12), an effective part of IL-12, interleukin 13 (IL-13), an effective part of IL-13, interleukin 15 (IL-15), an effective part of IL-15, granulocyte-macrophage colony stimulating factor (GM-CSF), an effective part of GM-CSF.

63. (Previously Added) The method according to claim 13, wherein the heat shock protein is selected from the group consisting of HSP70, an effective part of HSP70, HSP90, an effective part of HSP90, HSC70, an effective part of HSC70, GRP94, an effective part of GRP84, calreticulin (CRT), and an effective part of CRT.

64. (Previously Added) The method according to claim 14, wherein the third moiety is of lipid nature and is selected from the group consisting of a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

65. (Previously Added) The method according to claim 14, wherein the polyhydroxypolymer is a polysaccharide.

66. (Previously Added) The method according to claim 33 comprising at least 2 administrations per year.

67. (Previously Added) The method according to claim 66 comprising at least 3 administrations per year.

68. (New) The method according to claim 27, wherein the parenteral route is selected from the group consisting of the subcutaneous, the intracutaneous and the intramuscular route.